

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number  
**WO 2004/053057 A2**

(51) International Patent Classification<sup>7</sup>: C12N

(21) International Application Number:  
PCT/US2003/034563

(22) International Filing Date: 31 October 2003 (31.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/432,651 11 December 2002 (11.12.2002) US

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(81) Designated States (national): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,

CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

**Published:**

- without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/053057 A2

(54) Title: GENE EXPRESSION SYSTEMS AND RECOMBINANT CELL LINES

(57) Abstract: The present invention provides gene expression systems useful for detecting agonists of Toll-like receptors. The gene expression systems include a nucleic acid sequence encoding a Toll-like receptor and a second nucleic acid sequence that encodes a reporter operably linked to an expression control sequence. The recombinant cell lines include a gene expression system according to the present invention.

## GENE EXPRESSION SYSTEMS AND RECOMBINANT CELL LINES

### Background of the Invention

Cells of the immune system secrete a diverse set of compounds including  
5 cytokines, chemokines, co-stimulatory markers, and defensins in response to an immunological challenge.

Certain compounds known as immune response modifiers ("IRMs") possess potent immunostimulating activity including but not limited to antiviral and antitumor activity. Certain IRMs effect their immunostimulatory activity by, e.g., inducing the production and  
10 secretion of certain cytokines while inhibiting production and secretion of other cytokines. Certain IRMs are small organic molecules such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,482,936; 5,494,916; 6,110,929; 6,194,425; 4,988,815; 5,175,296; 5,367,076; 5,395,937; 5,693,811; 5,741,908; 5,238,944; 5,939,090; 6,245,776; 6,039,969; 6,083,969; 6,245,776; 6,331,539;  
15 and 6,376,669; and PCT Publications WO 00/76505; WO 00/76518; WO 02/46188, WO 02/46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; and WO 02/46194.

Additional small molecule IRMs include purine derivatives (such as those described in U.S. Patent Nos. 6,376,50 and 6,028,076), small heterocyclic compounds  
20 (such as those described in U.S. Patent No. 6,329,381), and amide derivatives (such as those described in U.S. Patent No. 6,069,149).

Other IRMs include large biological molecules such as oligonucleotide sequences. Some IRM oligonucleotide sequences contain cytosine-guanine dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,1994,388; 6,207,646; 6,239,116;  
25 6,339,068; and 6,406,705. Other IRM nucleotide sequences lack CpG and are described, for example, in International Patent Publication No. WO 00/75304.

Some of these IRMs induce cellular responses (e.g., the production and/or secretion of cytokines, chemokines, etc.) through one or more Toll-like receptors (TLRs). For example, certain small organic molecule IRMs are agonists of one or more of TLR-1,  
30 TLR-2, TLR-4, TLR-6, TLR-7, and TLR-8. Additionally, CpG has been reported to act through TLR 9.

In certain cells of the immune system, TLR activation can be associated with activation of the transcription factor NF- $\kappa$ B. NF- $\kappa$ B activation is associated with certain cellular responses to an immunological challenge, such as the production and secretion of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and MCP-1. IRM induction of such cellular responses can be demonstrated by measuring activation of the transcription factor NF- $\kappa$ B in response to exposing a cell to an IRM compound (See, e.g., Chuang *et al.*, *Journ. of Leuk. Biol.*, vol. 71, pp. 538-544 (2002), and Hemmi *et al.*, *Nature Immunology*, vol. 3(2), pp. 196-200 (2002)). Thus, NF- $\kappa$ B activation can be used as a reporter of TLR activation. However, the extent of NF- $\kappa$ B activation does not necessarily correlate with the extent of the downstream cellular response. This is so because the downstream cellular response may be modulated by one or more additional factors.

#### Summary of the Invention

The present invention provides an expression system that includes a first nucleic acid sequence that encodes a Toll-like receptor operably linked to a first expression control sequence; and a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter. In some embodiments, the first nucleic acid sequence and the second nucleic acid sequence are included on a single vector. In other embodiments, the first nucleic acid sequence and the second nucleic acid sequence are located on separate vectors.

In another aspect, the present invention provides a recombinant cell line that includes a host cell transfected with an expression system. In some embodiments, the expression system is contained within a single vector. In other embodiments, the expression system is contained among two or more vectors so that the host cell is co-transfected with all of the vectors of the expression system to obtain the recombinant cell line. In one embodiment, the host cell is a Namalwa cell.

In another aspect, the present invention provides a TLR agonist identified using either an expression system or a recombinant cell line according to the present invention.

In yet another aspect, the present invention provides pharmaceutical compositions including a TLR agonist identified using either an expression system or a recombinant cell line according to the present invention.

5 Various other features and advantages of the present invention should become readily apparent with reference to the following detailed description, examples, and appended claims. In several places throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

10 **Detailed Description of Illustrative Embodiments of the Invention**

The present invention provides gene expression systems and recombinant cell lines that may be useful for detecting TLR activation based on detecting induction of a downstream cellular response to TLR activation (e.g., production or secretion of one or more immune system compounds such as cytokines or co-stimulatory markers) rather than  
15 NF- $\kappa$ B activation. In some cases, the cellular response may be mediated by NF- $\kappa$ B, but in other cases the cellular response may be NF- $\kappa$ B-independent. Thus, the present invention provides gene expression systems and recombinant cell lines that may be useful for detecting a broader range of TLR activation than is possible by monitoring NF- $\kappa$ B activation. This may provide an ability to identify certain TLR agonists that would not be  
20 detected using an assay based on NF- $\kappa$ B activation. The gene expression systems and recombinant cell lines of the present invention also may provide a more relevant indication of the quantitative character of a particular cellular response to TLR activation by a particular TLR agonist.

In some cases, a gene expression system or recombinant cell line according to the  
25 present invention may be useful for detecting TLR activation that is not accompanied by NF- $\kappa$ B activation. Accordingly, the gene expression system and recombinant cell line may be employed to identify TLR agonists that do not necessarily also activate NF- $\kappa$ B. Such TLR agonists may be useful for treatment or prevention of certain conditions in which the production and secretion of pro-inflammatory cytokines such as those induced  
30 by NF- $\kappa$ B activation may be undesirable.

For purposes of this invention, the following terms shall have the meanings set forth.

“Activation” refers to modifying the indicated protein so that the protein provides a biological function. For example, TLR activation refers to modifying a TLR - for example, a conformational modification such as in response to exposure of the TLR to an agonist - so that the TLR is capable of inducing the production and secretion of certain  
5 cytokines.

“Agonist” refers to a compound that can combine with a receptor (e.g., a TLR) to produce a cellular response. An agonist may be a ligand that directly binds to the receptor. Alternatively, an agonist may combine with a receptor indirectly by, e.g., (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise results  
10 in the modification of another compound so that the other compound directly binds to the receptor. An agonist may be referred to as an agonist of a particular TLR (e.g., a TLR6 agonist).

“Amino acid sequence” refers to a particular ordered sequence of amino acids, whether naturally occurring or engineered.

15 “Co-transfect” and variations thereof refer to transfecting a host cell with more than one vector. A host cell may be co-transfected by transfecting with two or more vectors one at a time or in any convenient combination of vectors, including simultaneous transfection with all vectors.

“Express” and variations thereof refer to the ability of a cell to transcribe a structural gene to mRNA, then translate the mRNA to synthesize a protein that provides a detectable biological or biochemical function. “Expressible” refers to the ability of a particular nucleic acid sequence to be expressed by a cell that contains the nucleic acid  
20 sequence.

“Immune system compound” refers to any compound that is produced or secreted by cells of the immune system in response to an immunological challenge. Immune system compounds include but are not limited to cytokines, chemokines, co-stimulatory markers, and defensins.  
25

“IRM compound” refers to a compound that alters the level of one or more immune system compounds when administered to an IRM-responsive cell. Representative  
30 IRM compounds include the small organic molecules, purine derivatives, small heterocyclic compounds, amide derivatives, and oligonucleotide sequences described above.

“Nucleic acid sequence” refers generally to a region of DNA that has a definable function such as (a) encoding a peptide, polypeptide, or protein or (b) controlling expression of a nucleic acid sequence that encodes a peptide, polypeptide, or protein. For example, a nucleic acid sequence that encodes TLR6 refers generically to any sequence of  
5 nucleotides that encodes a TLR6 protein, without regard to (a) the species source of the nucleic acid sequence, (b) specific nucleotide sequence variants, or (c) whether such nucleotide sequence variants are naturally occurring or engineered.

“Nucleotide sequence” refers to a particular ordered sequence of nucleotide bases, whether naturally occurring or engineered.

10 It has been found that induction of certain secreted proteins or polypeptides can be useful as reporters of TLR activation. For example, IFN- $\alpha$  is a cytokine secreted by such immune system cells as T lymphocytes, macrophages, plasmacytoid monocytes, dendritic cells, and natural killer cells. IFN- $\alpha$  is involved in regulating a host's innate and adaptive immune responses to an immunological challenge, perhaps by providing a link between  
15 the two responses [Brassard *et al.*, *Journal of Leukocyte Biology* 71: 565-581 (2002)]. The innate immune response can include the cell-mediated response of natural killer (NK) cells to a non-self (e.g., neoplastic) or foreign (e.g., viral) antigen. IFN- $\alpha$  also may indirectly regulate the balance between Th1 and Th2 cell populations and, therefore, the innate and adaptive immune responses. Moreover, induction of IFN- $\alpha$  is independent of NF- $\kappa$ B  
20 activation.

Additionally, the production and secretion of NF- $\kappa$ B-dependent cytokines can be useful as reporters of cellular responses resulting from immunological challenge. Detection and measurement of such cytokines may provide comparative qualitative data regarding a cell's response to immunological challenge that is more relevant to an  
25 investigator than NF- $\kappa$ B activation data.

Thus, in certain embodiments, the present invention relates to recombinant cell lines and gene expression systems designed to assist detecting induction of immune system compounds and identification of compounds that induce expression of immune system compounds through TLRs.

30 Parts of the following description are provided in the context of IFN- $\alpha$  induction and detection. However, many of the features of the embodiments described below also may be realized using expression systems and recombinant cell lines designed to

specifically detect or induce other immune system compounds. Thus, expression systems and recombinant cell lines designed to specifically detect or induce immune system compounds other than IFN- $\alpha$  are explicitly included in the scope of the present invention.

5 The present invention provides a recombinant cell line capable of inducing gene expression from an expression control sequence of a gene that encodes an immune system compound (e.g., IFN- $\alpha$ ) in response to TLR activation. In some embodiments, for example, cells of the recombinant cell line, when exposed to a TLR agonist, can induce expression from an IFN- $\alpha$  promoter to a greater extent than cells of the corresponding untransfected cell line. Cells of the untransfected cell lines may substantially lack a  
10 functional level of TLR expression (i.e., untransfected cells may not detectably induce expression from the IFN- $\alpha$  promoter in response to exposure to a TLR agonist). Alternatively, cells of the untransfected cell line may exhibit a baseline level of background TLR function, but the baseline level is less than the level of TLR function observed in cells of the corresponding recombinant (i.e., transfected) cell line.

15 Cells of the recombinant cell lines include a first nucleic acid sequence that encodes a TLR operably linked to an expression control sequence. The cells also include a second nucleic acid sequence that encodes a reporter capable of generating a detectable signal when it is expressed in the recombinant cell under conditions suitable for generating the detectable signal. The reporter is linked to a second expression control sequence that  
20 is capable of being induced by activation of the TLR encoded by the first nucleic acid sequence.

The TLR encoded by the first nucleic acid sequence may be any TLR. Ten different human TLRs have been identified, cloned, and sequenced. TLRs also are known to exist in other mammals including, for example, mice and chimpanzees. The nucleotide  
25 sequences of the ten human TLRs and many non-human TLRs are known, have been published, and are readily accessible from various sequence databases including GenBank. The first nucleic acid sequence may include the nucleotide sequence of any one of the TLRs, whether human or non-human. In one embodiment, the TLR is human TLR6; in another embodiment, the TLR is human TLR7. Alternatively, the first nucleic acid may  
30 encode any one of the ten human TLRs, any non-human TLR, or any combination of two or more TLRs that may be desirable for a particular construct.

The first nucleic acid sequence can include a nucleotide sequence that differs from a specific published nucleotide sequence for the TLR encoded by the first nucleic acid sequence. For example, the first nucleic acid sequence can contain one or more substitutions (compared to a published TLR nucleotide sequence) that do not alter the amino acid sequence of the TLR protein expressed from the first nucleic acid sequence. Such a substitution may be termed a degenerate substitution. Nucleotide sequences containing one or more degenerate substitutions compared to a known TLR nucleotide sequence are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

As another example, certain nucleotide substitutions may alter the amino acid sequence of the TLR protein. For certain amino acid substitutions, however, the chemical properties of the protein having the altered amino acid sequence are similar to the chemical properties of the protein having the native amino acid sequence. Amino acids may be divided into four groups based on the chemical characteristics of the amino acid side groups: neutral, non-polar amino acids include glycine, alanine, valine, isoleucine, leucine, phenylalanine, proline, and methionine; neutral, polar amino acids include serine, threonine, tyrosine, tryptophan, asparagine, glutamine, and cysteine; acidic amino acids include aspartic acid and glutamic acid; and basic amino acids include lysine, arginine, and histidine. Substitution of one amino acid for another amino acid within the same group may have little or no functional effect on the resulting protein because of the similarity of the chemical characteristics of the amino acids involved in the substitution. Such amino acid substitutions may be termed a conservative amino acid substitution. Nucleotide sequences that, when compared to a known TLR nucleotide sequence, generate one or more conservative amino acid substitutions are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

The nucleic acid that encodes a TLR may be cloned into an expression vector so that it is under the expression control of its own promoter, a homologous TLR promoter, or any heterologous promoter inducible in an appropriate host cell. For example, in certain embodiments, the TLR6 structural gene may be cloned into the commercially available mammalian expression vector pCI-neo. In this case, the TLR6 structural gene may be cloned into the vector's cloning region using the *NheI* and *MluI* restrictions sites. In such an embodiment, after transfection of the vector into a mammalian cell, the TLR6

structural gene is under the transcriptional control of the vector's CMV enhancer/promoter region.

The second nucleic acid sequence encodes a reporter that is capable of generating a detectable signal when expressed in a host cell under conditions appropriate for generating the desired detectable signal. A wide variety of suitable reporter systems are known. For example, luciferase gene expression may generate a detectable luminescent signal under appropriate conditions. As another example,  $\beta$ -galactosidase expression can generate a detectable color change under appropriate conditions. As yet another example, production and secretion of an immune system compound may be detected by an enzyme-linked immunosorbent assay (ELISA). These and other reporter systems are known and assays for generating the detectable signals are commercially available.

The second nucleic acid sequence is operably linked to a second expression control sequence that includes a promoter sequence selected to be inducible by activation of the TLR encoded by the first nucleic acid sequence. Thus, expression and activation of the TLR encoded by the first nucleic acid sequence will induce gene expression from the second expression control sequence, thereby causing expression of the reporter, which may be detected by performing an assay designed to detect expression of the reporter. The second expression control sequence may include any suitable nucleotide sequence that can induce expression (e.g., a promoter) of a structural gene upon activation of the TLR encoded by the first nucleic acid sequence. Nucleotide sequences suitable for use as second expression control sequences include promoter sequences of TLR-inducible genes including but not limited to genes encoding cytokines, chemokines, co-stimulatory markers, and defensins. In certain embodiments, the second expression control sequence can include an IFN- $\alpha$ 1 promoter. When the reporter system being employed to detect TLR activation includes detecting production and secretion of an immune system compound with an appropriate ELISA assay, the second expression control sequence may include the promoter of the gene encoding the immune system compounds being expressed and detected as the reporter. However, in certain embodiments, it may be desirable to express the immune system compound from a heterologous promoter.

The first nucleic acid sequence and the second nucleic acid sequence may be contained within a single vector. Alternatively, the first nucleic acid sequence and the second nucleic acid sequence may be on separate vectors and co-transfected into a suitable

host cell. In certain embodiments, for example, the first nucleic acid sequence may be cloned into the pCI-neo vector as described above, while the second nucleic acid sequence can be cloned into a reporter vector. One example of a commercially available reporter vector is the pGL3-Enhancer vector, which includes a luciferase reporter gene downstream of a cloning site for cloning a promoter sequence of interest. In some embodiments, the promoter of a TLR-inducible immune system compound may be cloned into the pGL3-Enhancer cloning site. In one such embodiment, the IFN- $\alpha$  promoter may be cloned into the pGL3-Enhancer cloning site.

Suitable host cells include any transfectable cells capable of expressing exogenous mammalian genes. In some embodiments, the host cells may be mammalian cells such as human cells or mouse cells. For example, suitable host cells include human cells or descendants of a human cell including but not limited to Namalwa cells or HEK293 cells. Alternatively, the host cells may be mouse cells or descendants of a mouse cell including but not limited to RAW 264.7 cells.

In one embodiment, the host cells include Namalwa cells. Namalwa cells have certain characteristics that may be particularly desirable for certain embodiments of the present invention. For example, Namalwa cells can include an expressible chromosomal IFN- $\alpha$  gene locus. Thus, upon appropriate stimulation (e.g., viral infection), Namalwa cells can be induced to produce and secrete IFN- $\alpha$  from the chromosomal IFN- $\alpha$  gene locus. However, Namalwa cells do not naturally express certain TLRs (e.g., TLR6, TLR7, or TLR9). Certain agonists of such TLRs have been shown to induce IFN- $\alpha$  expression in other cell types (e.g., PMBCs), but may not induce IFN- $\alpha$  expression in Namalwa cells unless a functional level of TLR expression is provided.

Namalwa cells transfected with an expression system according to the present invention may be capable of expressing a functional level of the TLR provided by the expression system. Thus, Namalwa cells transfected with an expression system according to certain embodiments of the present invention may inducibly express IFN- $\alpha$  as a result of activating the cloned TLR (e.g., by exposure of the transfected Namalwa cells to an agonist). Thus, certain transfected cell lines of the present invention provide an ability to detect a TLR agonist by detecting TLR-mediated IFN- $\alpha$  expression by Namalwa cells. Such IFN- $\alpha$  expression may occur from the chromosomal IFN- $\alpha$  gene or from an IFN- $\alpha$  promoter cloned into the reporter vector.

Namalwa cells transfected with an expression system according to certain embodiments of the present invention can provide alternative means of detecting TLR expression. First, transfected Namalwa cells may generate a detectable signal as a result of expressing the reporter from the second expression control sequence, which may or  
5 may not include an IFN- $\alpha$  promoter (see Table 2). Second, transfected Namalwa cells may produce and secrete IFN- $\alpha$  from the chromosomal IFN- $\alpha$  gene locus. A transfected Namalwa cell line according to the present invention may be used to screen compounds in order to identify those compounds that induce TLR expression, i.e., TLR agonists.

Therefore, the present invention also provides TLR agonist compounds identified  
10 using an expression system or a recombinant cell line according to certain embodiments of the present invention. As described above, the expression systems and recombinant cell lines may provide the ability to identify TLR activation that may not be detectable using previously known TLR activation assays. A compound that induces TLR activity detectable by using a gene expression system or a recombinant cell line according to the  
15 present invention may be considered a TLR agonist. Such TLR agonists may include chemical structures similar in certain respects to the chemical structures of known IRM compounds. Alternatively, a gene expression system or a recombinant cell line according to the present invention may provide a tool for the screening (e.g., high throughput screening) chemically diverse compounds that may lead to the discovery of new TLR  
20 agonists, some of which may contain new chemical core structures capable of activating TLRs.

The present invention also provides pharmaceutical compositions containing a TLR agonist identified using an expression system or a recombinant cell line according to the present invention, or a pharmaceutically acceptable salt thereof, in an amount effective  
25 for inducing a TLR-mediated cellular response.

### Examples

The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however,  
30 that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention.

### Construction of vectors

The vector pIFN- $\alpha$ 1-luc was constructed by inserting BglII sites at both ends of the human IFN- $\alpha$ 1 promoter (SEQ ID NO:21). The BglII sites were inserted into the IFN- $\alpha$ 1 promoter and the sequence was amplified using the primer pair of SEQ ID NO:22 and SEQ ID NO:23. The amplified IFN- $\alpha$ 1 promoter was cloned into the pGL3-Enhancing vector (Promega Corp., Madison, WI) at its BglII site.

The vector pCI-TLR6 was constructed by inserting SEQ ID NO:11 (GenBank Accession No. NM 006068), which includes the human TLR6 coding sequence, into the pCI-neo mammalian expression vector (Promega Corp.) at the vector's NheI and MluI restriction sites.

### Transfections

Unless otherwise indicated, all incubations were performed at 37°C with 5% CO<sub>2</sub> at 98% humidity.

Culture medium was prepared from complete RPMI 1640 medium (BioSource International, Inc., Camarillo, CA). Fetal bovine serum (Atlas Biologicals, Inc., Ft. Collins, CO) was added to a final concentration of 7.5% (vol/vol); L-glutamine (BioSource International, Inc.) was added to 5 mM; and sodium pyruvate (BioSource International, Inc.) was added to 1 mM.

Burkitt's Lymphoma lymphoblastoid Namalwa cells (ATCC Accession No. CRL-1432) were grown by incubation in culture medium overnight. Cells were harvested by centrifugation in a tabletop centrifuge (1200 RPM for 5 minutes), and then resuspended in phosphate buffered sucrose to a concentration of  $1.3 \times 10^7$  cells per milliliter.

For each transfection, a 750  $\mu$ L aliquot of the cell suspension was placed in an electroporation cuvette with 4 mm gaps. 10  $\mu$ g of the pIFN- $\alpha$ 1-luc vector and 10  $\mu$ g of the pCI-TLR6 vector were added to the electroporation cuvette. The cell and vector mixtures were incubated at room temperature for 5 minutes. The cells were electroporated using a BioRad Gene Pulser (BioRad Laboratories, Hercules, CA) set to at 500  $\mu$ F capacitance and 0.27 volts, then incubated at room temperature for 5 minutes.

The electroporated cells were suspended in 10 mLs of culture medium and incubated overnight. Dead cells and debris were removed after 24 hours using a MACS

Dead Cell Removal kit (Miltenyi Biotec, Auburn, CA). Cells were resuspended in 10 mLs of culture medium and incubated for an additional 24 hours.

Transfected cells were selected by adding G418 (Promega Corp., Madison, WI) to a final concentration of 1 mg/mL and incubating the cells for seven days.

5

### Assays

The selected transfected cells were counted and resuspended to a concentration of  $1 \times 10^6$  cell per mL in culture medium. 100  $\mu$ L aliquots of cells were placed in the wells of a white-walled, white-bottomed 96-well plate (Corning, Inc. Corning, NY). 1.0  $\mu$ L of an IRM compound from Table 1 (prepared at 1 mM in 100% DMSO) was added to some cell aliquots so that the final concentration of IRM compound was 10  $\mu$ M. As a positive control, some cell aliquots were incubated with Sendai virus instead of IRM compound. As a negative control, some cell aliquots were incubated with DMSO without IRM compound. In all cases, the cells were incubated for 18 hours.

15

**Table 1 - IRM Compounds**

Compound	Chemical Name	Citation
IRM 1	4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-6,7,8,9-tetrahydro-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinoline-1-ethanol	U.S. 5,352,784 Example 91
IRM 2	4-amino- $\alpha,\alpha$ ,2-trimethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinoline-1-ethanol	U.S. 5,266,575 Example C1
IRM 3	N-[4-(4-amino-2-butyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl)butyl]methanesulfonamide	U.S. 6,331,539 Example 6
IRM 4	1-{2-[3-(3-pyridyl)propoxy]ethyl}-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-4-amine	WO 02/46193 Example 33
IRM 5	2-butyl-1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 39
IRM 6	2-butyl-6,7,8,9-tetrahydro-1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 40
IRM 7	N <sup>3</sup> -(4-[4-amino-2-(2-methoxyethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl]butyl)-6-(1 <i>H</i> -1-pyrrolyl)nicotinamide	U.S. 6,451,810 Example 60
IRM 8	2-ethyl-1-[5-(methylsulfonyl)pentyl]-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-4-amine	WO 02/46192 Example 13

The plates were equilibrated to room temperature before 1 volume of reconstituted LucLight Plus (Packard Instruments, Meriden, CT) was added to each aliquot of cells. Each well of the plate was read on an LJI Analyst (LJI Biosystems, Inc., Sunnyvale, CA) set with a 5 minute dark adapt. Data from a representative experiment are shown in Table 2. The data are expressed as the fold increase in luciferase induction off of the IFN- $\alpha$ 1 promoter in cell aliquots incubated with the indicated stimulant compared to the negative control in which the cell aliquots were incubated with only DMSO.

Table 2 - TLR Expression by pIFN- $\alpha$ 1-luc/pCI-TLR6 Co-Transfected Namalwa cells

<u>Stimulant</u>	<u>Fold Increase in Luciferase Induction</u>
IRM1	3.6
IRM2	2.7
IRM3	2.6
IRM4	4.0
IRM5	3.2
IRM6	2.9
IRM7	3.2
IRM8	2.3
Sendai virus	2.7

The complete disclosures of the patents, patent documents and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control.

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is Claimed is:

1. An expression system comprising:  
a first nucleic acid sequence that encodes a Toll-like receptor operably linked to a first expression control sequence; and  
5 a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter.  
10
2. The expression system of claim 1 wherein the second expression control sequence comprises an IFN- $\alpha$  promoter.
3. The expression system of claim 1 wherein the first nucleic acid sequence  
15 comprises the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, or a degenerate variant of any of the foregoing.
4. The expression system of claim 1 wherein the first nucleic acid sequence  
20 comprises a nucleotide sequence that encodes a polypeptide having the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, or any one of the foregoing sequences with one or more conservative amino acid substitutions.
- 25 5. The expression system of claim 1 wherein the detectable signal comprises luciferase activity or  $\beta$ -galactosidase activity.
6. The expression system of claim 1 wherein a first vector comprises the first nucleic acid sequence and a second vector comprises the second nucleic acid sequence.  
30
7. A vector comprising the expression system of claim 1.

8. A TLR agonist identified using the expression system of claim 1.
9. A pharmaceutical composition comprising the TLR agonist of claim 8, or a pharmaceutically acceptable salt thereof.
- 5 10. A cultured cell comprising the expression system of claim 1.
11. The cultured cell of claim 10 wherein the cell is a mammalian cell or a descendent of a mammalian cell.
- 10 12. The culture cell of claim 11 wherein the cell is a human cell or a descendent of a human cell.
13. The cultured cell of claim 10 further comprising an expressible nucleic acid  
15 sequence that encodes IFN- $\alpha$  operably linked to a third expression control sequence.
14. The cultured cell of claim 13 wherein the expressible nucleic acid sequence that encodes IFN- $\alpha$  is located on a chromosome of the cultured cell.
- 20 15. The cultured cell of claim 14 wherein the cultured cell is a Namalwa cell.
16. The cultured cell of claim 13 wherein the expressible nucleic acid sequence that encodes IFN- $\alpha$  is located on an extrachromosomal vector.
- 25 17. A TLR agonist identified using the cultured cell of claim 10.
18. A pharmaceutical composition comprising the TLR agonist of claim 17, or a pharmaceutically acceptable salt thereof.

30

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Ghosh, Tarun K.  
Fink, Jason R.

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Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln

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325

330

335

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58182US002.ST25.txt

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58182US002.ST25.txt

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 225 230 235 240  
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Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser  
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Val Ser Leu Phe Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe  
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Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly  
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Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val  
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Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu  
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Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu  
915 920 925

Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser  
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Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys  
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Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln  
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Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu  
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Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu  
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Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr  
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Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn  
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Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His  
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Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg  
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 Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu  
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 Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu  
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 Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu  
 225 230 235 240  
 Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn  
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 Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly  
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 Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe  
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 Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser  
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 Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser  
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 420 425 430

Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln  
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Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile  
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Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu  
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Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp  
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Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn  
 Page 39

58182US002.ST25.txt  
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645

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Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser  
705 710 715 720

His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser  
725 730 735

Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn  
740 745 750

Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu  
755 760 765

Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg  
770 775 780

Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp  
785 790 795 800

Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser  
805 810 815

Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe  
820 825 830

Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala  
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His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu  
850 855 860

Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr  
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Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe  
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Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe  
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Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile  
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Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu  
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Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro  
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Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu  
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Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn  
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## 58182US002.ST25.txt

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 145 150 155 160  
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 165 170 175  
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 180 185 190  
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 Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu  
 225 230 235 240  
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 Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe  
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 Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly  
 275 280 285  
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 Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu  
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58182US002.ST25.txt

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 385 390 395 400

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Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu  
 420 425 430

Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu  
 435 440 445

Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu  
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Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser  
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His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val  
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Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu  
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Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr  
 565 570 575

Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser  
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Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn  
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595

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605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe  
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Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu  
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Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala  
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Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala  
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Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser  
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Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp  
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Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val  
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Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu  
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His Asn Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys  
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Glu Leu Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr  
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 Cys Ser Trp Pro Glu Thr Val Val Asn Met Asn Leu Ser Tyr Asn Lys  
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